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In this issue

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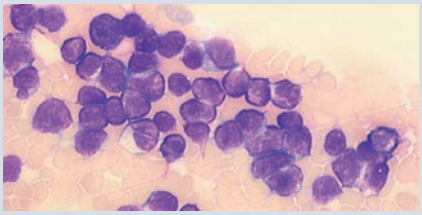
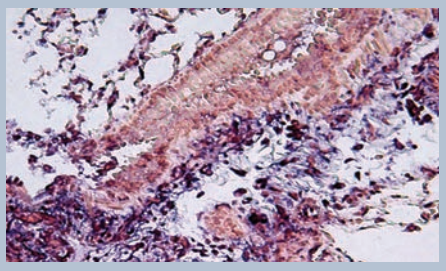
Acute myeloid leukemia (AML) is frequently caused by genetic alterations that affect transcription factors, such as *AML1-ETO*, and mutations affecting genes involved in signal transduction pathways, such as *FLT3*. Mutations in *AML1-ETO* and *FLT3* length mutation (*FLT3-LM*) are 2 of the most common genetic alterations seen in patients with AML, but neither mutation alone can cause leukemia in animal models. In this issue, Schessl et al. report that *AML1-ETO* cooperates with *FLT3-LM*, causing hematopoietic progenitor cells to become malignant and potently triggering rapid and aggressive acute leukemia in mice (pages 2159–2168). Further, the authors report that in 135 patients with AML1-ETO–positive AML, the most common additional mutations found affected signal transduction genes. These data directly support a pathogenetic model of acute leukemia, according to which an activating mutation in a signal transduction pathway and a mutation in a transcription factor are required for leukemogenesis. This insight into the collaboration of 2 complementary classes of oncogenes in AML has direct implications for therapeutic interventions as it forms the rationale to test signal transduction inhibitors in AML1-ETO–positive leukemias with additional activating mutations of receptor tyrosine kinases.



Common protein found to be novel proinflammatory factor

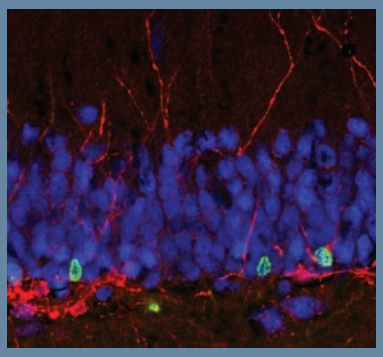


Biglycan is a small, leucine-rich proteoglycan that is a component of the extracellular matrix and found abundantly in many tissues, but its biological function was unknown. In this issue of the *JCI*, Schaefer et al. (pages 2223–2233) show that biglycan is an integral part of the innate immune system and a crucial proinflammatory factor. The researchers demonstrate that biglycan is released during inflammation and acts as an endogenous ligand of Toll-like receptor 4 in macrophages. Biglycan increases macrophage responses, which leads to rapid activation of p38 and p42/44 MAPKs and NF-κB and boosts expression of TNF-α and macrophage inflammatory protein–2. The researchers also show that mice lacking biglycan have a considerable survival benefit in experimental sepsis due to lower levels of circulating TNF-α and reduced infiltration of mononuclear cells in the lungs. Finally, macrophages synthesize biglycan when exposed to proinflammatory factors. These results show that the matrix component biglycan is not only a signaling molecule and a proinflammatory factor but also a potentially new therapeutic target for the treatment of sepsis.

HIV domains take on new functions in mediating immunity

HIV evades the host immune system by downregulating $CD4^+$ immune T cell function, which aids infection. Now, Quintana et al. examine the fusion peptide (FP) of HIV in order to reveal the mechanisms underlying this phenomenon (pages 2083–2098). The researchers show that the FP plays 2 roles in HIV infection — it works with other domains to mediate fusion of the virus with the cell membrane, while also downregulating the T cell responses that normally would block infection. The authors show that the HIV FP colocalizes with CD4 and T cell receptor in T cells and inhibits antigen-specific T cell proliferation. These data highlight a potential immunosuppressive activity specific to HIV infection. The authors extend their findings by showing that treatment with FP ameliorates the autoimmune disease adjuvant arthritis in rats. This study not only adds to our understanding of the mechanisms of HIV pathogenesis but also shows that the FP molecule, independent of HIV, could be exploited to decrease undesirable immune responses.

G-CSF strikes hard at stroke and drives neurogenesis



Stroke is a major medical problem for which there are only very limited treatment options. In this issue of the *JCI*, Schneider, et al. describe surprising new roles for G-CSF in the central nervous system, including its potential for treating stroke (pages 2083–2098). G-CSF was known to be a potent hematopoietic factor that acts on cells of the myeloid lineage. Now researchers report that G-CSF has potent cell-protective effects on mature neurons and drives neuronal differentiation of adult neural stem cells in the brain. G-CSF doubles hippocampal neurogenesis, even in normal, nonischemic animals. Moreover, G-CSF has profound beneficial effects on long-term functional outcome after experimental cerebral ischemia. The authors show that G-CSF itself is a neuronally expressed protein in the brain and that systemically given G-CSF can penetrate the intact blood-brain barrier, which makes it a potentially novel treatment for stroke and a candidate for diseases where disturbances in neurogenesis are a probable factor.